UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#4G4295 -- Abamectin (AGRI-MEK/AVID 0.15 EC Miticide/Insecticide) for Use in/on Potatoes. Merck & Co.'s Submission Dated 11/24/93. EPA Reg. Nos. 618-98/618-96.

DP Barcode: D199136. CBTS # 13203.
MRID #: 430352-01 (6 volumes).

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Merck & Co., Inc. is proposing a temporary tolerance of 0.002 ppm for residues of the insecticide abamectin (avermectin B_1) and its delta 8,9-isomer in/on potatoes. The temporary tolerance petition is associated with an EUP request for the period April 1, 1994 - December 31, 1994. A total of 505 acres in 18 states would be treated with 30.3 lbs active ingredient.

Permanent tolerances for residues of avermectin B_1 and its delta 8,9 geometric isomer have been established under 40 CFR 180.449 on tomatoes (0.01 ppm) and under §186.300 on tomato pomace (0.07 ppm). Tolerances on apples, citrus, citrus pulp,

citrus oil, and cottonseed have expired. Tolerances on cattle fat (0.01 ppm), cattle meat and meat byproducts (0.02 ppm) and milk (0.005 ppm) have also expired. Permanent tolerances are pending on these and a number of other racs.

Conclusions

1. The petitioner should confirm that the seasonal maximum use level for abamectin in/on potatoes is 0.0585 lb ai/A (3 x 0.0195 lb ai/A). The summary document, page 003, implies that the maximum (1x) rate is 6 x 0.0195 lb ai/A. Because our conclusion concerning the proposed temporary tolerance is unaffected -- residue data are available under exaggerated rates -- this information may be submitted as part of the permanent tolerance petition.

2. The nature of the residue in plants and animals is adequately understood for purposes of this temporary tolerance petition. The residue to be regulated is avermectin B_{1a}, avermectin B_{1b} and the delta 8,9 isomer of avermectin B_{1a}. For permanent tolerances, any use resulting in a significant increase in residues could require a new ruminant metabolism study using a C-14 label. For the permanent tolerance petition, animal metabolism will be reassessed upon receipt of additional residue data and a processing study.

3a. Analytical methods are available in the Pesticide Analytical Manual, Volume II (PAM II) for tolerance enforcement of abamectin in/on potatoes. However, the method used to generate the residue data, although similar to the enforcement methods, is simpler and should be submitted to PAM II as a letter method.

3b. Avermectin $B_{1a,1b}$ and the delta 8,9 isomer are not recovered under FDA's multiresidue protocols.

4. Potato samples were analyzed within six weeks of sampling. Available storage stability data on other RACs are quite sufficient to support the residue analyses. For a permanent tolerance, samples analyzed over longer time periods will require supporting storage stability data on potatoes.

5. Residue data from four field trials support the absence of residues at the detection limit of each component of the residue (0.002 ppm). However, the temporary tolerance should be set at the limit of quantitation -- 0.005 ppm -- not the limit of detection. A revised Section F is needed. For a permanent tolerance,

additional residue data will be necessary. If residues of avermectin remain below the method's limit of quantitation, an additional 8 field trials will be necessary in Regions II (1), V (2), IX (1), X (1) and XI (3). If quantifiable residues are found in any sample, an additional four trials will be necessary in Regions V (2) and XI (2). (Geographic regions are defined in Attachment 2). In each of these field trials, the EC formulation should be applied at a 1x rate and two composite samples analyzed per site.

6. No potato processing study has been submitted in this petition. For purposes of the requested temporary tolerance, such a study is not necessary. For permanent tolerances, potatoes harvested from plants receiving an exaggerated rate should be processed into dry and wet peels. (Processing into dried flakes/ granules is not necessary due to the absence of quantifiable residues in/on tubers following exaggerated treatment levels in the four field trials.)

7a. Based on submitted residue data, tolerances (expired) in meat and milk will not be exceeded due to the proposed use. This conclusion will be reassessed in evaluation of the permanent tolerance petition, when additional residue data and a processing study have been submitted.

7b. Potatoes or potato processed products are not poultry feed items. Tolerances for poultry commodities are not necessary from the proposed use.

8. An International Residue Limits (IRL) Status sheet is appended to this review. There are no Codex, Canadian or Mexican maximum residue limits for abamectin in/on potatoes. Compatibility is therefore not an issue.

Recommendation

Provided that a revised Section F is submitted (see Conclusion 5), and TOX considerations permitting, CBTS recommends in favor of a temporary tolerance of 0.005 ppm for residues of abamectin and its delta 8,9 isomer in/on potatoes. A DRES analysis can be carried out using this value.

NOTE TO PM: The tolerances for meat, fat, meat byproducts and milk for which we recommended previously (but which expired in 1993) should be reestablished prior to or simultaneously with the tolerance on potatoes.

Detailed Considerations

Manufacture and Formulation

Abamectin (avermectin B_1) is produced by a fermentation process. The manufacturing process was reviewed in detail in L. Cheng's memo dated 5/1/86 for EPA 618-0L. Abamectin is a mixture of two avermectins. Avermectin B_{1a} contains a sec-butyl group at the C-25 position; avermectin B_{1b} contains an isopropyl group. The technical product contains at least four times the concentration of the B_{1a} as the B_{1b}. The structure is given as Attachment 1.

The TGAI consists of about 95% avermectin. The formulation proposed for use in/on potatoes is AGRI-MEC 0.15 EC, an emulsifiable concentrate containing 0.15 lb. active ingredient (ai) per gallon.

Proposed Use

For control of the twospotted spider mite, Colorado potato beetle, *Liriomyza* leaf miner. Apply in 10-50 gallons of finished spray per acre (ground) or 2-10 gallons per acre (air). Do not exceed 16 fl. oz. of AGRI-MEK per acre (0.0195 lbs ai/A) per application or 48 fl. oz. per acre in a growing season. Do not apply at less than 7 day intervals. Do not apply within 14 days of harvest. Do not apply this product through any type of irrigation system. Do not graze or feed treated foliage to livestock.

The summary document dated 11/24/93 states (page 003) that "The proposed tolerance is based upon the maximum use rate of 0.0195 pounds of active ingredient per acre (16 fluid ounces) with six (6) applications at one week intervals and a fourteen (14) day preharvest interval." As summarized below, the minimum application rate for the four field trials was 0.0195 lb ai/A x 6. According to the proposed label, this should represent a 2x seasonal rate not a 1x rate. The petitioner should clarify this issue and revise its Section B, if necessary.

We note that potato foliage is not listed as an animal feed item in Table II of our Residue Chemistry Guidelines. It is not necessary that a grazing/feeding restriction appear on the label.

Nature of the Residue

Plants. No new plant metabolism information has been submitted with this petition. Metabolism studies have been submitted for cotton/cottonseed (PP#5G3500), citrus (PP#5G3287), and celery (PP#8F3649). Plant metabolism has been discussed in various CBTS memos, including, among others, memo of C. Deyrup, 7/29/87, for

PP#7F3500; memo of V.F. Boyd, 8/5/88, for PP#'s 8F3592 (citrus) and 7F3500; and memo of V.F. Boyd, 11/16/88, for PP#8F3649. In the three RACs studied, avermectin was extensively metabolized into a number of polar degradates. NMR and MS studies have shown that these degradates do not contain the macrocylic lactone ring -- which apparently accounts for the observed toxicity. Toxicological studies on polar degradates obtained by photodegradation indicated no major toxicity, and CBTS concluded that the photodegradates were sufficiently similar to those obtained in the RAC metabolism studies. The nature of the residue in the three RACs is understood. The residue to be regulated is parent avermectin and its delta 8,9 isomer. This residue typically constitutes less than ten percent of the total residue resulting from application of avermectin.

Because the observed metabolism is qualitatively similar in three dissimilar crops, we do not consider a fourth study on potatoes to be warranted at this time. The residue to be regulated is avermectin B_{1a}, avermectin B_{1b} and the delta 8,9 isomer of avermectin B_{1a}.

Animals. No new metabolism studies were submitted with this petition. Metabolism studies on rats and goats were reviewed by L. Cheng in his 2/11/87 memo for P#7G3468/FAP#7H5518 and later by C. Deyrup in her 7/29/87 memo for PP#7F3500. Three groups of two goats each were dosed with 0.005, 0.05 and 1 mg ^{3}H-avermectin B_1 per day for ten days. At the dose level of 1 mg/day, the maximum total residue observed was 98 ppb in liver. Levels in muscle were lower than 10 ppb. The principal component of the residue was determined to be avermectin B_1. The major metabolite -- present at up to 43% of the residue in kidney -- was 24-hydroxymethyl avermectin B_1.

As summarized in V.F. Boyd's memo of 6/21/89 for PP#8F3592, CBTS and TOX concluded that the hydroxymethyl metabolite need not be regulated because (1) tolerance levels of 0.02 ppm for meat and meat byproducts and 0.005 ppm for milk were sufficiently high to include any metabolite residues and (2) the toxicity of this metabolite should not exceed that of the parent. However they also concluded that if the tolerances for residues in meat and milk needed to be raised at some future time, the metabolite might have to be included in the tolerance expression.

The other major issue regarding the goat metabolism study was the registrant's use of a tritium label instead of the normal C-14 label. Potential problems associated with the use of this label were discussed in C. Deyrup's 7/29/87 memo. CBTS finally concluded (PP#7F3500, memo of V.F. Boyd, 1/4/89) that

> These data from the H^3-AVM goat studies are considered an adequate description of the nature of the residue in

ruminants for assessing lower limit residues of AVM in feed (i.e., cottonseed) ....which would contribute only 1.25 ppb AVM residues to the diet of beef cattle.

Any use resulting in a significant increase of residues could require a new ruminant metabolism study using a C-14 label. For purposes of this temporary tolerance petition, the nature of the residue in ruminants is adequately understood. The residue to be regulated is avermectin B_{1a}, avermectin B_{1b} and the delta 8,9 isomer of avermectin B_{1a}. For a permanent tolerance on potatoes the metabolism will be reassessed pending receipt of additional residue data and a processing study.

Neither potatoes nor potato processed products are poultry feed items. Poultry metabolism is not relevant to this petition.

Analytical Methods

The analytical method used in the analysis of potatoes for residues of avermectin B_1 and its delta 8,9-isomer is Merck Method No. 936-92-4: HPLC-Fluorescence Determination for Avermectin B1 and its Delta-8,9 Isomer in Raw Whole Potatoes; July 25, 1992; Tway, P.C., Wehner, T.A., Payne, L.D., Egan, R.S., and Escudero, C.J. The method appears on page 979 (vol. 6) in the six volume report of potato field trials (MRID # 430352-01) and was independently validated by Analytical Development Corporation (ADC), Colorado Springs, CO. ADC also analyzed potato samples from the field trials.

A 5.0-g potato sample is homogenized in methanol, then reextracted with methanol. The extracts are made aqueous (≥70%) and loaded onto a C8 solid-phase extraction (SPE) column, which is piggybacked with a NH_2 SPE column. Avermectins are eluted with 10 mL of methanol. The sample is split; half is taken to dryness and reconstituted with 1.0 mL acetonitrile. The other half is saved for repeat analysis, if necessary. Samples and standards are derivatized with 1-methylimidazole and TFAA:ACN (1:2). Samples and standards are diluted appropriately with ACN and analyzed for avermectin B1 by reversed phase HPLC with fluorescence detection (excitation at 365 nm, emission at 418 nm). The derivatized residue quantitated represents the sum of avermectin B1 and its delta 8,9 isomer. (The structure of the derivatized product is given as Attachment 1 to this memo.) The claimed limit of detection is 2.0 ng/g; the limit of quantitation is 5.0 ng/g.

Validation by ADC showed the following recoveries:

Table 1

Percent Recoveries from Potatoes Fortified With Avermectin B_{1a}, B_{1a}-Delta-8,9, or Avermectin B_{1b} (n=5 for each fortification level)

	Fortification Level ng/g	Percent Recovery
B_{1a}	5.0	95±3.1
	25.0	82.6±0.9
	100	86.0±7.0
B_{1a}-D89	5.0	96.4±10.2
	25.0	86.0±3.9
	50.0	77.0±3.5
B_{1b}	5.0	84.8±6.7

It should be noted that the delta-8,9 isomer of avermectin B_{1a} and avermectin B_{1b} are quantitated using the standard curve prepared with avermectin B_{1a}. This issue was addressed by J. Stokes (PP#1F3787, memo of 4/16/92) and G. Herndon (PP#1F3787, memo of 12/16/93). Quantitation of avermectin B_{1b} using the B_{1a} curve accurately measures residues up to 100 ng/g. Regarding the delta- 8,9 isomer, the actual fluorescent derivative is identical to that formed from B_{1a}.

Two methods for avermectin in plant matrices have undergone successful EPA method validation -- Merck Method No. 1009, for citrus, and Method No. 8000, for pears. Method 6004, for ginned cottonseed, has been submitted to PAM II as a letter method. All these methods have essentially the same derivatization, chromatography (HPLC) and fluorescent detection steps. They differ in extraction and cleanup. The method for citrus involves extraction with methanol, filtration and washing of the filtrate with isooctane. To the methanol extract (about 50 mL) is added 250 mL 10% NaCl, and the resulting solution is partitioned with a 0.01% t-butanol in $MeCl_2$ solution. The solution is then dried over sodium sulfate and concentrated to 2-3 mL. Methylene chloride is added to bring the volume to 10 mL and the solution split for repeat analysis, if necessary. The remaining one-half of the sample is concentrated to less than 1 mL and cleaned up on an alumina column. The avermectin and its isomer are then reacted with TFA/DMF/1-methylimidazole followed by methanolic ammonium hydroxide. The derivative and standards are taken up in chloroform, cleaned up on a silica column, taken to dryness, and then re-dissolved in 5 mL MeOH for HPLC analysis. (PP#7G3468,

Jay Wilner, memo of 9/30/87)

In the method for ginned cottonseed, residues of avermectin and its delta 8,9 isomer are extracted with methanol and the filtered extract passed thorough an aminopropyl column. The methanol solution is made 10% aqueous with saline and then washed with isooctane. More saline is added and the solution is partitioned with 0.01% t-butanol in methylene chloride. The organic extract is concentrated and methanol added. The solution is made aqueous and passed through a C8 column. Avermectin residues are eluted with ethanol. Ethyl acetate, water, and ammonium hydroxide are added to the ethanol eluant and the resultant solution extracted with isooctane. The isooctane layer is concentrated and then partitioned between acetonitrile and hexane. The acetonitrile fraction is concentrated and reacted with DMF/TFA/1-methylimidazole followed by ammonium hydroxide/methanol to form the fluorescent derivative. Chloroform is added to the mixture which is then passed through a silica gel column to remove excess reagents. The purified solution is evaporated, taken up in methanol, and analyzed by HPLC with fluorescent detection. (C. Deyrup, PP#7F3500, memo of 7/29/87)

The method for pears includes an enzymatic extraction and will not be discussed further.

The new method for avermectin residues in potatoes is clearly simpler than the methods for residues in citrus or ginned cottonseed and should be submitted as a letter method to PAM II. Both the citrus and the cottonseed method should quantitate avermectin B_1 and its delta 8,9 isomer, but the many additional partitioning steps could result in some losses. The petitioner may wish to amend the methods previously submitted to PAM II. The derivatization procedure is much simpler in the latest method.

Avermectin is not recovered when tested under FDA's multiresidue protocols.

Magnitude of Residue

Storage Stability. Samples from the four field trials were analyzed within six weeks of harvest. Storage stability data reflecting stability of avermectin B_{1a}, B_{1b} and the delta 8,9 isomer of avermectin B_{1a} are available on pears for one year (PP#9F3787, J. Stokes, memo of 7/9/91); celery for two years (PP#8F3649, S. Willett, memo of 5/4/90); oranges, lemons and grapefruits for one year (PP#8F3592, V.F. Boyd, memo of 6/21/89); tomatoes for six months (PP#9F3703, S. Willett, memo of 12/15/89); and cottonseed (parent only) for 14 months (PP#7F3500, C. Deyrup, memo of 7/29/87). These data are more than adequate

to support the potato residue data, but additional residue data reflecting longer periods in storage should be supported by storage stability data on potatoes.

Residue Data. Residue data from four field trials appear in the following report:

> "Determination of the Magnitude of Residues of Abamectin and its Delta 8,9 Isomer in/on the Raw Agricultural Commodity Potatoes from Abamectin 0.15 EC Applied with Parafinic Crop Oil by Ground Equipment;" J.A. Norton; 11/17/93; Study ID No. 618-936-3671. (MRID # 430352-01)

Field trials were carried out in NY, PA, OR and FL. Abamectin 0.15 EC was ground applied in six applications about one week apart. The NY, PA and OR trials received 6 x 0.10 lb ai/A (10 x the label seasonal maximum). In these trials the pesticide was applied at 30 gallons per acre both with and without addition of a crop oil. Samples were taken 0, 3, 7 and 14 days after final application. In the Florida trial, 6 x 0.019 lb ai/A (2x the label seasonal maximum) was applied in 50 gallons per acre with a crop oil. Samples were taken 0 and 14 days after application. In all the field trials two independent composites were taken after each application regimen.

The complete set of chromatograms has been submitted. Neither avermectin B_{1b}, nor B_{1a}, nor the delta 8,9 isomer were present at the detection limit of 2 ppb, but in some of the chromatograms from treated samples peaks were present at the retention time of avermectin B_{1a}. If the peaks were due to avermectin, the concentration would be about 1 ppb.

The data support the absence of residues at the limit of detection (0.002 ppm) for each component of the residue. However, the temporary tolerance should be set at the limit of quantitation -- 0.005 ppm -- not the limit of detection. For a permanent tolerance additional residue data will be necessary. If residues of avermectin remain below the method's limit of quantitation, an additional 8 field trials will be necessary in Regions II (1), V (2), IX (1), X (1) and XI (3). However, if quantifiable residues are found, an additional four trials will be necessary in Regions V (2) and XI (2). Please see Attachment 2 for the definition of geographic regions. In each of these field trials, the EC formulation should be applied at a 1x rate and two composite samples analyzed per site.

Processing Study

Processed commodities for potatoes include granules/flakes; chips; peel, wet; and peel, dried. No potato processing study has been submitted with this petition. For purposes of this

temporary tolerance petition, processing data are not necessary.

According to our Rejection Rate Analysis guidance for maximum theoretical concentration factors, issued 2/93, the maximum concentration factor (experimental) for potatoes is greater than 30. On the other hand the theoretical concentration factor based on loss of water for dried flakes/granules is 4.7. Since three of the residue trials were carried out at a 10X rate, processing into flakes/granules is not necessary. However, potatoes harvested from plants receiving an exaggerated rate should be processed into dry and wet peels for the permanent tolerance petition.

Meat, Milk, Poultry and Eggs

According to our updated Table II (April, 1994) to our Residue Chemistry Guidelines, potato culls may constitute up to 75% of the diet of beef cattle and 50% of the diet of dairy cattle. Processed potato waste may constitute the same percentages. (Processed potato waste residues can be estimated from residues on the rac by application of the maximum concentration factor for wet/dry peels.)

Results of a 28-day cattle feeding study were submitted in PP#7G3468 and were reviewed by L. Cheng in his memo of 2/11/87. Dairy cows were dosed at 10, 30 or 100 ppb with avermectin B_1. At the 100 ppb level, the maximum level observed in tissue was 20 ppb in liver; the maximum level in milk was 4 ppb. Using a diet consisting of cottonseed, cottonseed meal, cottonseed hulls, citrus pulp and corn, V.F. Boyd estimated that the maximum concentrations in the diet of beef cattle and dairy cattle would be 36 ppb and 35 ppb, respectively, leading to an estimated maximum residue in cattle of 9 ppb in liver and 2 ppb in milk (PP#8F3592, memo of 6/21/89). Replacement of cottonseed or citrus by cull potatoes would result in a lower estimated concentration in the diet. Temporary tolerances (which have expired) for meat and milk will therefore not be exceeded. CBTS had previously recommended that permanent tolerances on meat and milk be established (PP#8F3592, memo of V.F. Boyd, 8/8/89). These tolerances should be reestablished prior to or simultaneously with the tolerance on potatoes. We do note that the pending use in/on almonds and walnuts would require an increase in the tolerance for abamectin in fat from 0.01 to 0.015 ppm (PP#1F3973, G. Herndon, memo of 11/26/91). In the permanent tolerance petition the contribution of processed potato waste to the diet of ruminants needs to be assessed.

Other Considerations

An International Residue Limits Status sheet is appended to this review (Attachment 3). There are no Codex, Canadian or

Mexican maximum residue limits for abamectin in/on potatoes. Compatibility is therefore not an issue.

Attachments:
1. Structures of avermectin B_1 and its fluorescent derivative.
2. Definition of Geographic Regions (3 pages).
3. IRL Status sheet.

cc: RF, Circu., PP#4G2495, Mike Flood, E. Haeberer.
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